

Official Title of the study: Breathing Meditation Intervention for Posttraumatic Stress Disorder
NCT02366403

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Key Design Features:

- Noninferiority design comparing a breathing-based meditation (SKY; Sudarshan Kriya Yoga) to VA standard of care (CPT-C; cognitive processing therapy-cognitive only) in treating PTSD.
- Primary outcome measure: PTSD Check List (PCL-C)
- Randomized 92 Veterans: SKY (n=46) and CPT-C (n=46).
 - 7 Excluded Post Randomization (4 ineligible; 1 forgot hearing aid; 2 course cancelled)
- Intent to Treat Analysis N=85; SKY (n=41) and CPT-C (n=44)
- Per protocol 59 completers SKY (n=30) and CPT-C (n=29)
- Symptoms measured at Baseline, end of treatment, 1 month and 1 year.

Statistical Plan

Preliminary analyses will compare the two treatment groups (SKY, CPT-C) across key variables including age, education, gender, psychiatric comorbidity (depression, etc), and severity of posttraumatic stress disorder (total CAPS score), using t-tests or chi-squared tests. The treatment groups are not expected to differ on key variables due to adequate randomization. However, if significant between-group differences are found, appropriate sub-groups of patients will be included in all subsequent analyses.

ITT and per protocol

In the ITT analysis, all participants who are randomized will be included and we will use the “last observation carried forward” methodology which is considered a conservative approach for handling missing data (ICHE10, 2006; Piaggio et al., 2006; Streiner & Geddes, 2001). As this approach favors the alternative hypothesis in a noninferiority design, we will also use a per-protocol approach, which favors the null hypothesis. Lowering the alpha level to correct for multiple comparisons is not appropriate in noninferiority designs as it has the same effect as increasing the alpha level in traditional (superiority) designs.

Hypothesis 1: We hypothesize that both SKY and CPT-C will decrease PTSD symptom severity at EOT as measured by the PCL-C (noninferiority hypothesis). The noninferiority margin is 10 points or less on the PCL-C. Following recommendations for analyzing noninferiority designs (Greene et al., 2009) we will use both confidence interval testing and hypothesis testing. For **confidence interval testing**, we will calculate the mean change in PCL-C scores from baseline to EOT for SKY (Δ SKY) and CPT-C (Δ CPT-C) groups. We will then estimate the difference between the means of the two populations i.e., (Δ CPT-C) - (Δ SKY) using the formula for a 95% C.I. for the difference in the means of two populations (unpaired) samples data. This formula uses a weighted average of the sample variances from the two groups and is a pooled estimate of the common variance of the two populations. If the 95% C.I. of this value lies between 0 and 10, we will reject the null hypothesis and conclude that the SKY

treatment is not inferior to the CPT-C treatment. For the **hypothesis testing**, we will test for the difference in the means of two populations of unpaired data to compare the two values $\Delta\text{CPT-C}$ and ΔSKY using a one-sided t-test ($\alpha = 0.025$). Again, we will use a pooled estimate of the common variance of the two populations. If the critical t-value is met, we will reject the null hypothesis.

Hypothesis 2: We hypothesize that both SKY and CPT-C will show similar drop-out rates by EOT. Dropout has no well-established benchmark needed to establish a noninferiority margin therefore we will simply compare dropout frequencies across groups. The definition of treatment dropout, taken from previous PTSD trials, e.g., (Rizvi et al, 2009) is completing <75% of the treatment sessions. Randomization should control for many factors that may influence dropout. However, higher dropout is linked to younger age and lower education (Rizvi et al, 2009). As these variables can vary widely in our study, dropout rates will be compared using binary logistic regression in which the outcome variable (dropout; yes/no) will be compared across treatment groups using age and education as covariates.

Dropouts will be examined from two definitions: 1) those who failed to complete 75% of sessions, and 2) those who attended the first session, and failed to complete 75% of sessions.

Hypothesis 3: We hypothesize that the effects of SKY will not be clinically inferior to the standard CPT-C treatment at 1 month and 1 year follow-ups. We will test these noninferiority hypotheses separately for each time point vs. baseline in the same way as described for the PCL-C at EOT (Hypothesis 1) using the PCL-C, Beck Depression Inventory BDI-II, and PANAS. Noninferiority margin for the PCL-C will be ≤ 10 points (see Hypothesis 1), for the BDI-II, will be ≤ 3 points (Button et al, 2015), and for the PANAS will be ≤ 3 points (Watson, Clark, & Tellegen, 1988). Both confidence interval testing and hypothesis testing will be used.

Hypothesis 4 (exploratory): Not necessary for primary outcome paper We hypothesize that SKY intervention will improve PTSD symptoms more in Veterans suffering from exaggerated arousal as measured by increased heart rate (HR). Additionally, for Veterans with more cognitive symptoms (e.g., memory and attention impairments) we expect the CPT-C intervention to be more effective. **To test the first hypothesis**, we will perform a regression analysis to compare the change in PTSD symptoms from baseline to EOT [PCL-C baseline – PCL-C EOT] to the baseline HR (mean beats per minute) for each treatment group. Using the regression model, we will test for an interaction between HR and treatment. We expect to find that high baseline HR is associated with more improvements in PTSD symptoms in the SKY group than the CPT-C group. **To test the second hypothesis** we will calculate a baseline cognitive z-score as described above to yield a composite cognitive score (Zcognitive) for each participant. A regression analysis will compare the change in PTSD symptoms from baseline to EOT [PCL baseline – PCL EOT] with Zcognitive for each treatment group. Using the regression model, we will test for an interaction between Zcognitive and treatment. We expect to find that low baseline cognitive scores are associated with more improvements in PTSD symptoms in the CPT-C group than the SKY group.

Timeline

Analysis	Sept 2019	Oct 2019	Nov 2019	March 2020	TBD
Preliminary Analyses	X				
Hypothesis 1 ITT and per protocol	X				
Hypothesis 2 ITT only		X			
Hypothesis 3 ITT and per protocol			X (EOT and 1 month FU)		
Hypothesis 3 ITT and per protocol				X 1 year FU	
Hypothesis 4					X Timeline depends on data availability